REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 30-34, and 42-49 are pending after entry of the amendments set forth herein.

Claims 30-34, 36-40, and 42-44 were examined. Claims 30-34, 36-40, and 42-44 were rejected. No claims were allowed.

Claims 30, 34, and 42 are amended. Support for theses amendments is found in the claims as originally filed, as well as in the specification at, for example, page 22, line 28 though page 23, line 16.

Claim 45-50 has been added. Support for new claims 45-49 is found in the claims as originally filed, as well as in the specification at, for example, page 26, line 29 through page 28, line 11, and page 58, lines 4-30.

The specification and the abstract have been amended to address the objections raised by the Examiner. The specification has been amended on page 57, line 16-17 to correct the incomplete sentence. Support for the amended material can be found in the specification, for example, at page 11, lines 7-8.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

Restriction Requirement

Applicants acknowledge that claims 30-44 are withdrawn from consideration as being drawn to non-elected invention.

Sequence Compliance

The objections based on the compliance of the application with the Sequence Listing rules have been addressed by the amendment of September 15, 2003. Withdrawal of these objections is respectfully requested.

Specification

The specification has been amended to address the objections raised by the Examiner. Withdrawal of these objections is respectfully requested.

Rejection under 35 U.S.C. § 112 first paragraph

Claims 30-34, 36-40, and 42-44 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification failed to enable the claimed invention.

Without conceding as to the correctness of this ground of rejection, Applicants note that claims 36-40 have been cancelled, rendering the rejection moot as applied to these claims. Furthermore, applicants have amended the claims for clarification. The claims now require that the viral vector be delivered subretinally or intravitreally, and that this delivery results in production of the angiogenic factor in the eye and induction of neovascularization. This rejection is traversed as it may be applied to the claims as presently pending.

The law is clear that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." United States v. Telectronics, Inc., 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). See also, Genentech, Inc. v. Novo Nordisk, 42 USPQ 2d 1001 (Fed. Cir. 1997), cert. denied, 522 U.S. 963 (1997); Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991). .

Furthermore, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 227 USPQ 428 (Fed. Cir. 1985). See also, MPEP §2164.01. Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, in Hybritech v. Monoclonal Antibodies, Inc. (231 USPQ 81 (Fed. Cir. 1986)) the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.

The Examiner asserts that the specification only provides enablement for a non-human animal model of neovascularization produced by subretinal delivery of a rAAV vector encoding a VEGF

transgene (with respect to claims 30-34 and 36-40), and a method for using the model for determining the ability of an anti-angiogenic factor to inhibit the onset of neovascularization by co-administering rAAV vectors encoding VEGF and an anti-angiogenic factor (with respect to claims 42-44).

As Applicants understand it, the rejection is based on the assertion that the specification does not provide enablement for:

(1) use of any angiogenic transgene (e.g., Office Action, page 5, first full paragraph);

(2) use of any gene delivery means (e.g., Office Action, text bottom of page 5 to top page 7);

(3) delivery of the transgene to any part of the eye (e.g., Office Action first full paragraph page 7); and

(4) a method to determine the ability of an anti-angiogenic factor to inhibit neovascularization at all stages of the disease and in a patient (Office Action page 8m second paragraph).

These same grounds are reiterated at several points throughout the rejection set out in the Office Action from page 3 to page 12. These various aspects of the rejection are addressed below.

A. Use of any angiogenic transgene

The Office Action emphasizes that the specification fails to provide guidance that correlates the administration of any angiogenic factor other then VEGF with neovascularization in a non-human animal as encompassed by claims 30-33, 36-39 and 42-44.

It is well established that neovascularization of the eye is synonymous with the phenomenon of angiogenesis (see Adamis et al., *Angiogenesis* 1999, (3)1:9-14; see Exhibit A). Although only VEGF has been described in a working example as noted by the Examiner, it was well known in the art at the time of filing of the present application that other angiogenic factors function in induction of angiogenesis. Several research publications prior to the filing of the present application show that the link between various angiogenic factors and angiogenesis was known.

For example, Ozaki et al., Opthalmic Res. 1996, 28(6):356-360 (Exhibit B), observed increased levels of angiogenin in the vitreous of patients with proliferative diabetic retinopathy, which is known to involve neovascularization. As such, it is reasonable to conclude that once neovascularization activity of an angiogenic factor such as VEGF was established by the present inventors, other angiogenic factors

would be expected to similarly cause neovascularization. Therefore, Applicants respectfully submit that the disclosure in conjunction with the relevant art is enabling for the full scope of the claims.

B. Use of any gene delivery means

Claims 30-33, 36-39, and 40-42 were also rejected on the grounds that the specification allegedly does not teach delivery of the angiogenic factor-encoding nucleic acid using any virus other then an adeno-associated virus. The Office Action further asserted that the field of viral-mediated gene delivery is highly unpredictable, and, in view of this unpredictability, the specification, in conjunction with the art, fails to provide guidance for delivery of an angiogenic factor using any viral-delivery vector other then AAV.

In support, the Office Action cites Verma et al. (Nature, 1997, 389:239-242), and states that each gene delivery vector has characteristic limitations, therefore a vector should be chosen according to desired parameters (Office Action, page 6) . Additionally, the Office Action cited Eck et al. (Goodman and Gillman's The Pharmacological Basic of Therapeutics, 1996, 77-101) to show that the level of protein function necessary to complement a defect varies among genetic disease. However, neither of these references suggests that the field is *so unpredictable* that one skilled in the art could never achieve success. Rather, the cited references provide further guidance to one skilled in the art in practicing the claimed invention. For example, Verma establishes that in order to achieve success in using viral gene delivery vectors, various factors must be taken into consideration prior to selecting the appropriate vector. Similarly, Eck establishes that the level of protein expression required varies between different genetic defects; therefore such differences must be taken into consideration in selecting the appropriate vector as well as the gene of interest. This guidance actually serves to *reduce* the amount of work the ordinarily skilled person would need to undertake to practice the claimed invention.

In addition, the specification on pages 13-17, provides detailed instructions on using various viral gene delivery methods other then adeno-associated viral vector. For instance, the specification provides instructions, as well references, for using retroviral vectors, alpharvirus vectors, as well as other gene delivery vectors such as pox viruses, SV40, influenza virus, herpes virus, HIV, and measles.

C. Delivery of the transgene to any part of the eye

Additionally, the Office Action states that the specification does not enable delivery of the angiogenic factor to any site other then the subretinal space. However, on pages 26-28 of the present application, the specification provides detailed information regarding administering gene delivery vectors to the various subsections of the eye. On page 27, lines 19-30, applicants detail the viral titer calculations required to determine the quantity of gene delivery vector required for retinal delivery. Furthermore, on page 28, lines 6-11, the specification provides that the gene delivery vectors may also be administered to the intraocular region of the eye, and further provides an acceptable dosage range. In addition, on page 56, "Example 16" clearly establishes that delivery of VEGF produces subretinal as well as choroidal neovascularization.

Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[1] Furthermore, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[2] As noted by Examiner in the outstanding Office Action, the present application does contain working an example demonstrating neovascularization by subretinal delivery of an angiogenic factor. In view of this guidance, applicants respectfully submit that the enablement requirement is satisfied.

D. Method to determine the ability of an anti-angiogenic factor to inhibit neovascularization

The Office Action also rejects claims 42-44 on the grounds that the specification allegedly fails to provide adequate teachings or guidance for the testing of factors for the inhibition of neovascularization at all stages of the disease. The Office Action stresses that the specification provides no teachings or guidance as to how to correlate the results presented in the specification with the inhibition of ongoing neovascular disease in a patient. The Examiner does note that the specification provides enablement for evaluating the effectiveness of an anti-angiogenic factor in preventing neovascularization in a non-human animal model.

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1. *In re Borkowski,* 164 USPQ 640 at 645.

The Examiner also rejects claims 42-44 for lacking enablement because the specification allegedly fails to provide adequate teaching with regard to inhibition of neovascularization in an individual by using the recited method to carry out gene therapy.

Applicants submit that the methods of claims 42-44 are directed to decreasing or preventing neovascular disease in a non-human animal model, not a patient. This method is directed to *screening for anti-angiogenic factors that have a desired effect.* The specification provides an example of at least one such anti-angiogenic factor that has a desired effect, thus showing that the animal model is susceptible to use in the claimed screening method.

In view of the above, applicants respectfully request that the rejections of claims 30-34 and 42-44 under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection under 35 U.S.C. § 112 second paragraph

Claims 36-40 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Without conceding as to the correctness of the grounds of this rejection, claims 36-40 have been canceled, rendering this rejection moot.

Rejection under 35 U.S.C. § 102

Claims 30, 31, 33, and 34 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Okamoto et al., American Journal of Pathology, 1997, 151:281-291 (*hereinafter* "Okamoto"). This rejection is traversed as it may be applied to the pending claims.

As noted by Examiner on page 13 of the outstanding Office Action, Okamoto teaches a transgenic non-human animal model for neovascularization of the retina produced by the expression of VEGF. However, the non-human animal model of the present invention is not transgenic for VEGF, but is modified so that the nucleic acid encoding the angiogenic factor is present primarily or only in the eye. This is accomplished by subretinal or intravitreal delivery of the viral vector containing the

2. *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

angiogenic factor-encoding nucleic acid. In contrast, the transgenic animal of Okamoto is modified so that the VEGF-encoding construct is present in all or nearly all the cells of the animal.

Since Okamoto discloses a transgenic non-human model rather then a non-human model produced by intravitreal or subretinal delivery of a viral construct encoding an angiogenic factor, the cited reference fails to disclose each and every element of the presently amended claims. Accordingly, withdrawal of this rejection of claims 30, 31, 33, and 34 is respectfully request.

Rejection under 35 U.S.C. § 103

Claims 36, 37, 39, and 40 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Okamoto in view of Rakoczy et al., Drug Dev. Res., 46:277-285 (*hereinafter* "Rakoczy"), and Tomidokoro et al., Eye Res., 18:381-390 (hereinafter "Tomidokoro"). Without conceding as to the correctness of this ground of rejection, claims 36, 37, 39 and 40 have been cancelled, rendering this rejection moot.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number BERK-010DIV.

Respectfully submitted,
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Date: Nov. 13, 2003

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